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PAPER

"*In silico*" mechanistic studies as predictive tools in microwave-assisted organic synthesis†

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Computational calculations can be used as a predictive tool in Microwave-Assisted Organic Synthesis (MAOS). A DFT study on Intramolecular Diels–Alder reactions (IMDA) indicated that the activation energy of the reaction and the polarity of the stationary points are two fundamental parameters to determine "*a priori*" if a reaction can be improved by using microwave irradiation.

Introduction

Computational chemistry,[1] more commonly known as theoretical chemistry or molecular modelling, is a field that has undergone spectacular development in recent decades. The term theoretical chemistry was defined as the mathematical description of chemistry. However, the term computational chemistry is generally used when a mathematical method is sufficiently well developed that it can be automated for implementation on a computer.

The application of quantum mechanics to organic chemistry dates back to Hückel's π-electron model[2] of the 1930s. Approximate quantum mechanical treatments for organic molecules continued throughout the 1950s and 1960s with, for example, PPP, CNDO, MNDO and related models. Application of *ab initio* approaches, such as Hartree–Fock theory,[3] began in the 1970s and flourished in the mid-1980s, with the development of computer codes that allowed the automated optimization of ground and transition states and the incorporation of different electron correlation functions using configuration interaction or perturbation techniques. The release by Pople's group of Gaussian-70,[4] the first full-featured quantum chemistry computer package that was used by a broad range of researchers, enabled the growth of this discipline. In this regard, given the broad array of theoretical tools now available, computational calculations represent a useful approach to study and understand certain chemistry problems. Indeed, the synergy between theory and experiment has vastly accelerated progress in many areas.

A good indicator of the increasing importance of computational methods for organic chemists is the large number of articles published in the last few decades. This statistical evidence shows that the use of computational chemistry continues to grow in the organic community. Computational methods have had a great impact on our current understanding of organic chemistry and this methodology has played a significant role in developing new theories and providing important supporting evidence for experimentally derived insights.

Our research group has maintained an interest in the computational study of microwave-assisted reactions in order to understand and predict the effects of microwave irradiation in organic synthesis. In general we have studied: (a) the determination of molecular orbitals and their atomic coefficient values,[5] (b) the influence of catalysts,[6] (c) modifications in the regio- and stereoselectivity under microwave irradiation,[7] (d) the occurrence of thermal and non-thermal effects through the determination of the thermodynamic and kinetic parameters of the reaction.[8]

As a continuation of our previous studies, we report a computational investigation into intramolecular Diels–Alder cycloaddition reactions (IMDA). The aim was to determine the energetic and physical parameters required to improve a reaction under microwave irradiation and to use these calculations as predictive tools. We selected two previously reported IMDA reactions: (i) cycloaddition reactions of *N*-alkyl-2-cyano-1-azadienes,[9] (ii) hetero-Diels–Alder reactions of (1*H*)-pyrazinones in ionic liquid-doped solvents.[10] These reactions were chosen because they require long reaction times at high temperatures and sometimes high pressures. The applicability of Diels–Alder reactions is limited by the reversibility of the reaction when long reaction times are required. All of these problems can be conveniently solved by the rapid heating produced by microwave irradiation, a situation not easily accessible by classical methods. Despite the fact that some of these processes have been described in the literature[11] under classical heating, there are no computational studies aiming to explain the role of microwave irradiation on the course of IMDA reactions.

Calculation methods

All calculations included in this paper were carried out using the GAUSSIAN 03[12] series of programs, with the standard 6-31G* basis set.[13] In order to include electron correlation at a reasonable computational cost, Density Functional Theory

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(DFT)[14] was used. These calculations were carried out by means of the three-parameter functional developed by Becke *et al.*,[15] which is usually denoted as B3LYP. Zero-point vibrational energies (ZPVEs) were computed at the B3LYP/6-31G* level and were not scaled. All transition structures and minima were fully characterized by harmonic analysis. For each located transition structure, only one imaginary frequency was obtained in the diagonalized Hessian matrix, and the corresponding vibration was found to be associated with nuclear motion along the reaction coordinate. Reaction paths were checked by intrinsic reaction coordinate (IRC) calculations.[16] Solvent effects were estimated by means of polarization continuum models (PCM)[17] using benzene, chlorobenzene and dichloroethane (DCE) as solvents.

The molecular hardness (η) of each species was computed according to the following approximate expression (eqn (1)).

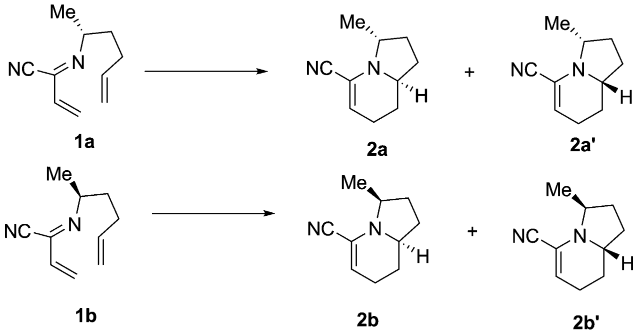
$$\eta = \frac{1}{2}(\varepsilon_L - \varepsilon_H) \qquad (1)$$

Where ε_L and ε_H are the energies of the LUMO and HOMO, respectively.

Results and discussion

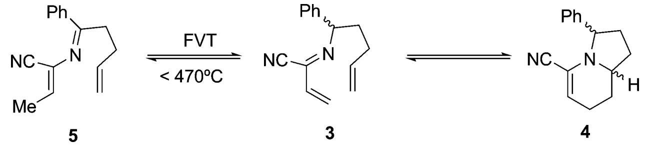
Intramolecular Diels–Alder reaction of *N*-alkyl-2-cyano-1-azadienes

Fowler and col.[9] reported that IMDA reactions of 2-cyano-substituted *N*-alkylazadienes **1** generated fused bicyclic nitrogen heterocycles **2** (Scheme 1). Indolizines **2** were obtained as a 4 : 1 mixture of diastereomers by heating overnight in benzene in a sealed tube at 100 °C.[18] This long reaction time could be reduced to 14 min when IMDA reactions were carried out in a microwave oven (650 W). Moreover, a different diastereomeric ratio was found (2.2 : 1).



Scheme 1

Heating a solution of **3** in benzene did not result in the intramolecular cycloaddition to give indolizine derivative **4** regardless of the mode of heating. NMR experiments revealed that decomposition of the starting material occurs. However, the use of flash vacuum thermolysis at 470 °C (Scheme 2), where the azadiene is brought into the gas phase by cosublimation with benzene, gave a very clean conversion to the desired Diels–Alder product **4** (mixture of *cis*/*trans* isomers). However, at a slightly lower temperature (400 °C) the reaction took a different course and produced 2-azadiene **5** (Scheme 2).



Scheme 2

In order to clarify why this process was improved under microwave irradiation we carried out a computational study on the IMDA reaction. All possible intermediates and transition states for the reaction paths were optimized at the B3LYP/6-31G* level and the solvent effect was determined at the B3LYP(PCM)/6-31G* level, considering benzene as the solvent.

Initially, we explored the potential energy surface of the IMDA reaction shown in Scheme 1 by studying the cycloaddition of both enantiomers **1a** and **1b**. It is noteworthy that the most stable conformation does not correspond to the reactive conformation and, consequently, a conformational change occurs before the reaction takes place. The two conformations for both enantiomers are depicted in Fig. 1.

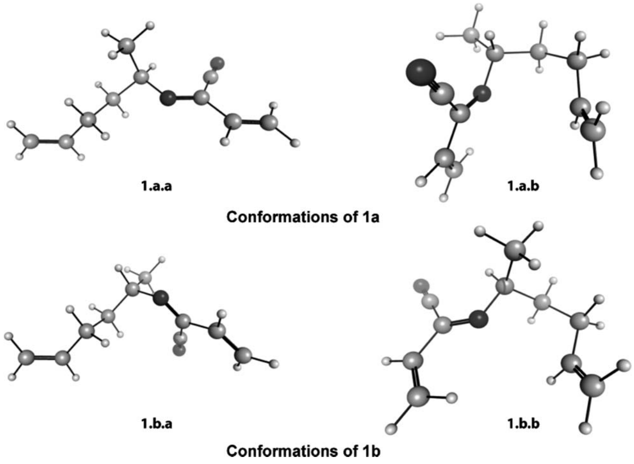


Fig. 1 Most stable (a) and reactive (b) conformations of compounds **1a** and **1b**.

The presence of one stereocentre in position 3 produces two diastereomeric Diels–Alder adducts. The origin of these two stereoisomers is relatively complex since both diene and dienophile have diastereotopic faces. This situation allows four possible diastereomeric reaction paths, two passing through *exo* and two through *endo* transition states (*endo-supra*, *exo-supra*, *endo-infra*, *exo-infra*). However, because inversion of the nitrogen atom occurs rapidly at room temperature, *cis* and *trans* ring fusions are not possible and it is not possible to distinguish between *exo* and *endo* transition states. Therefore, we only considered two approaches: *endo-supra* and *endo-infra*. The main features of the transition structures of these approaches are shown in Fig. 2.

From a structural viewpoint, the reaction must occur through a synchronous process since the two critical distances are very similar.

We computed the energy parameters and some physical properties of this reaction in order to investigate the origin of the improvement under microwave irradiation. Calculated energy parameters are collected in Table 1 and physical properties

Table 1 IMDA reaction of compound **1**. Activation energy (ΔEa, kcal mol^{-1}), Gibbs energy (ΔG, kcal mol^{-1}) and enthalpy energy (ΔH, kcal mol^{-1}) computed at B3LYP(PCM)/6-31G*+ΔZPVE

Entry	Reaction	ΔEa	ΔG	ΔH	Products
1	**1a** → **2a**	22.61	−25.25	−30.13	**2a** (*R*,*R*)
	1a → **2a′**	28.59	−25.95	−30.75	**2a′** (*R*,*S*)
2	**1b** → **2b**	24.83	−27.12	−32.26	**2b** (*S*,*R*)
	1b → **2b′**	18.86	−26.42	−31.64	**2b′** (*S*,*S*)

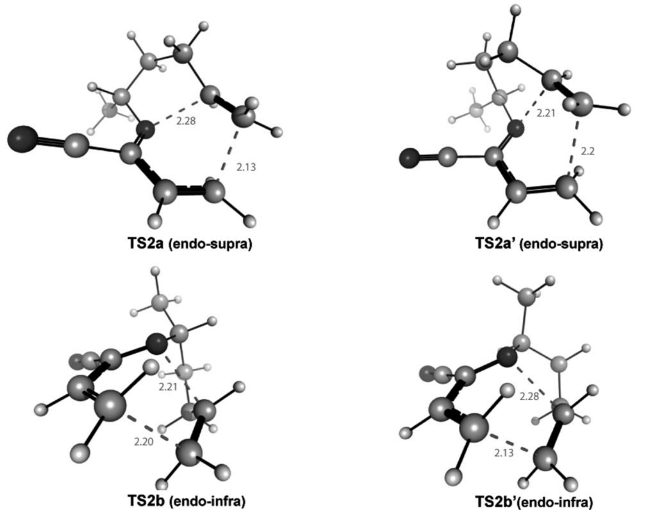


Fig. 2 Main features of the transition states computed at the B3LYP(PCM)/6-31G* level of theory corresponding to the IMDA reaction of compound **1**.

(hardness, polarity, polarizability and volume values) for all the species involved in the reaction are given in Table 2.

Our results indicate that a high activation energy is required to perform this IMDA reaction (Table 1) (18.86–28.59 kcal mol^{-1}). The reaction is also very exothermic and has a high Gibbs energy. These outcomes confirm that reactions with high activation energies (20–30 kcal mol^{-1}) can be improved under microwave irradiation due to overheating or hot spots.[8]

It is remarkable that the most stable approaches correspond to transitions states with the chain substituent in the opposite face to where the cycloaddition takes place. These are **TS2a** for the *R*-enantiomer and **TS2b′** for the *S*-enantiomer. These results are in agreement with the experimental outcomes. As a result, the major racemate has an (*R*,*R*)-(*S*,*S*) configuration. It's noteworthy, that the different values of the physical properties for each enantiomer pair are due to the consideration of the different conformations for both enantiomers in each pair.

Table 2 IMDA reaction of compound **1**. Volume (*a*0, Å), dipole moments (μ, D), average polarizability volumes (α'_{av}, Bohr^3), hardnesses (η, eV) of reagents, transition structures and products computed at B3LYP(PCM)/6-31G*+ΔZPVE

Entry	Stationary point	*a*0(Å)	μ (D)	α'_{av} (Bohr^3)	η (eV)	$\Delta\mu$ (D)
1	**1a**	4.71	2.22	134.91	0.086	
2	**1b**	4.94	1.97	131.57	0.086	
3	**TS2a**	4.87	5.08	141.40	0.077	2.86
4	**TS2a′**	4.7	4.51	138.55	0.078	2.30
5	**TS2b**	4.63	4.51	138.54	0.078	2.54
6	**TS2b′**	4.89	5.08	141.41	0.077	3.10
7	**2a**	4.74	5.38	126.38	0.086	
8	**2a′**	4.52	5.40	125.53	0.087	
9	**2b**	4.67	5.40	125.53	0.087	
10	**2b′**	4.76	5.38	126.39	0.086	

Loupy and Perreux reported a rationalization of microwave effects in organic synthesis based on medium effects and mechanistic considerations.[19] In this respect, a polar medium (reactants, solvent or susceptors) results in acceleration due to an increase in material–wave interactions during the course of the reaction. Furthermore, reactions with hard, polar, or poorly polarizable[20] transitions states or reactions in which the polarity increases from the ground to the transition state can be improved under microwave irradiation. We calculated these physical properties for all species involved (Table 2) in order to ascertain whether the IMDA reaction follows these conditions.

Analysis of the results shows that the most significant parameter is the polarity. It is noteworthy that **TS2a** and **TS2b′**, which are energetically most favoured, are also the most polar (Table 2, entrie 3 *vs.* 4 and 6 *vs.* 5 and 6). This fact is not consistent with the experimental results, since in this case a large diastereomeric excess is expected under microwaves but does not occur experimentally. These transition states are also the most polarizable, in contradiction with some previously published results.[20] In this IMDA reaction the polarity increases along the reaction coordinate from the ground to the transition state. On the basis of this information, energetic parameters and the polarity increase can explain the improvement found in this reaction under microwave irradiation.

We subsequently carried out a computational study of the IMDA cycloaddition of compound **3**. This reaction did not take place with either conventional heating or under microwave irradiation. However, under harsh conditions, *i.e.* flash vacuum thermolysis at 470 °C, a very clean conversion to the desired Diels–Alder product **4** was achieved.

Calculated energy parameters and physical properties are collected in Tables 3 and 4, respectively.

Again, the different conformations for enantiomers possess different values for the physical properties. In this case, the major racemate has an (*R*,*S*)-(*S*,*R*) configuration. The high calculated activation energies (23.52–33.10 kcal mol^{-1}) explain why the reaction does not occur under conventional heating or microwave irradiation. As we reported previously, this result shows that activation energies close to, or higher than 30 kcal mol^{-1}, are not accessible under microwave irradiation and require harsher conditions. Moreover, Gibbs energies associated with this process are markedly lower than those in the reaction of compound **1**. This could be due to the higher steric hindrance of the phenyl group, which leads to an increase in the entropy of the system, with the consequent decrease in the Gibbs energy (ΔG values collected in Table 3 *vs.* Table 1) and the reaction rate.

Table 3 IMDA reaction of compound **3**. Activation energy (ΔEa, kcal mol^{-1}), Gibbs energy (ΔG, kcal mol^{-1}) and enthalpy energy (ΔH, kcal mol^{-1}) computed at B3LYP(PCM)/6-31G*+ΔZPVE

Entry	Reaction	ΔEa	ΔG	ΔH	Products
1	**3a** → **4a**	32.91	−16.60	−31.93	**4a** (*R*,*R*)
	3a → **4a′**	23.52	−14.99	−31.97	**4a′** (*R*,*S*)
2	**3b** → **4b**	23.73	−14.84	−31.95	**4b** (*S*,*R*)
	3b → **4b′**	33.10	−16.11	−31.92	**4b′** (*S*,*S*)

Table 4 IMDA reaction of compound **3**. Volume (*a*0, Å), dipole moments (μ, D), average polarizability volumes (α'_{av}, Bohr^3), hardnesses (η, eV) of reagents, transition structures and products computed at B3LYP(PCM)/6-31G*+ΔZPVE

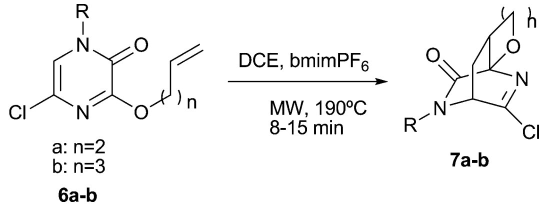
Entry	Stationary point	*a*0 (Å)	μ (D)	α'_{av} (Bohr^3)	η (eV)	$\Delta\mu$ (D)
1	**3a**	5.22	2.57	191.46	0.083	
2	**3b**	5.17	2.27	190.08	0.082	
3	**TS4a**	5.01	4.89	172.45	0.075	2.32
4	**TS4a′**	5.23	5.11	197.47	0.077	2.54
5	**TS4b**	5.08	5.11	197.48	0.077	2.84
6	**TS4b′**	5.05	4.89	196.56	0.075	2.62
7	**4a**	4.98	5.26	180.16	0.086	
8	**4a′**	4.83	5.35	180.73	0.087	
9	**4b**	5.03	5.34	180.71	0.087	
10	**4b′**	5.02	5.26	180.12	0.086	

Experimentally, it was found that at 400 °C the reaction took a different course and produced 2-azadiene **5**. This process is probably reversible at higher temperature to produce the cycloadduct. Our theoretical studies show that isomer **5** is 12 kcal mol^{-1} more stable than diene **3**, so the isomerization is the more feasible reaction. In contrast, a similar compound (with a methyl group) is 8.4 kcal mol^{-1} more stable than **1**. Therefore, in this case the higher speed of the IMDA reaction prevents the isomerization.

Intra- and intermolecular Diels–Alder reactions of 2(1*H*)-pyrazinones in ionic liquid-doped solvents

In the second part of this study we selected an inter- and intramolecular hetero-Diels–Alder cycloaddition involving 2(1*H*)-pyrazinone. Kappe and col.[10] explored the potential of microwave irradiation in the presence of an ionic liquid in these reactions. In some cases significant rate enhancements were observed on comparing the standard protocols to the microwave-heated transformations, while in other cases less marked improvements were found.

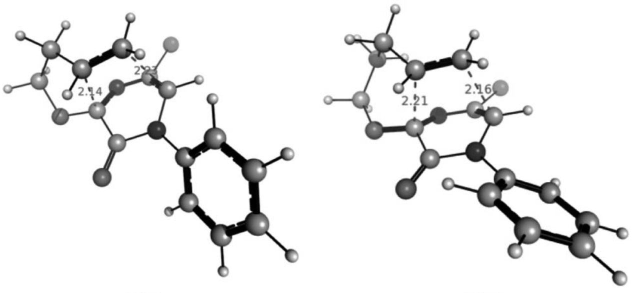
The first reaction involved is the intramolecular hetero-Diels–Alder reaction of alkenyl-tethered 2(1*H*)-pyrazinones **6a–b** (Scheme 3).



Scheme 3

The reaction mixture was irradiated in a single-mode microwave cavity using a preselected maximum temperature of 190 °C (300 W maximum power), dichloroethane (DCE) and 0.035 mmol of 1-butyl-3-methylimidazolium hexafluorophosphate (bmimPF$_6$) in a sealed vessel. The reaction took place within 10 min and gave good yields (67–77%). Thus, under these conditions the complete conversion of **6** took place in *ca.* 8–10 min, which represents a considerable shortening of the reaction time compared to the 1–2 days required under conventional reflux in chlorobenzene. The authors postulate that the rapid heating and the high temperatures achieved are possible for three reasons: (a) the 2(1*H*)-pyrazinone acts as a "molecular radiator",[19,21,22] itself absorbing some of the microwave energy; (b) DCE couples with microwaves reasonably well because its loss-tangent (tan δ) is similar to that of water; (c) the ionic liquid is able to change the dielectric properties of an otherwise less polar solvent and this is sufficient to achieve more rapid heating to higher reaction temperatures. In general, it is known that ionic liquids can be used as microwave susceptors[23] and their use in small amounts allows very rapid heating by microwaves. Due to their ionic nature, ionic liquids couple very effectively with microwaves through an ionic conduction mechanism.

In this framework, we performed a computational study on the IMDA reaction. We explored the potential surface of this reaction at the B3LYP(PCM)/6-31G*+ΔZPVE level using DCE as solvent. The main features of the transition structures involved are depicted in Fig. 3. Energetic features and physical properties of these compounds are collected in Tables 5 and 6.



TS7a

TS7b

Fig. 3 Main features of the transition states computed at the B3LYP(PCM)/6-31G* level of theory corresponding to the IMDA reaction of compound **6**.

Table 5 IMDA reaction of compound **6**. Activation energy (Δ*E*a, kcal mol^{-1}), Gibbs energy (Δ*G*, kcal mol^{-1}) and enthalpy energy (Δ*H*, kcal mol^{-1}) computed at B3LYP(PCM)/6-31G*+ΔZPVE

Entry	Reaction	Δ*E*a	Δ*G*	Δ*H*	Products
1	**6a** → **7a** *exo*	28.27	0.84	−7.48	**7a**
2	**6a** → **7a′** *endo*	25.72	−2.27	−8.92	**7a′**
3	**6b** → **7b** *exo*	39.68	−1.24	−8.93	**7b**
4	**6b** → **7b′** *endo*	37.25	−1.54	−8.80	**7b′**

Table 6 IMDA reaction of compound **6**. Volume (*a*0, Å), dipole moments (μ, D), average polarizability volumes (α'_{av}, Bohr^3), hardnesses (η, eV) of reagents, transition structures and products computed at B3LYP(PCM)/6-31G*+ΔZPVE

Entry	Stationary point	*a*0 (Å)	μ (D)	α'_{av} (Bohr^3)	η (eV)	$\Delta\mu$ (D)
1	**6a**	5.16	5.23	226.64	0.077	
2	**6b**	5.65	5.11	239.88	0.098	
3	**TS7a**	5.28	6.62	229.63	0.083	1.39
4	**TS7a′**	5.34	6.09	228.21	0.090	0.86
5	**TS7b**	5.01	6.46	244.30	0.083	1.35
6	**TS7b′**	5.11	5.36	242.71	0.087	0.25
7	**7a**	4.77	7.37	208.63	0.098	
8	**7a′**	5.36	7.19	209.04	0.099	
9	**7b**	5.20	7.00	222.26	0.099	
10	**7b′**	4.93	6.90	222.52	0.099	

From a structural and energetic viewpoint, *endo* approaches are preferred in both cases (Table 5, entries 2 *vs.* 1, and 4 *vs.* 3) and these processes therefore require high energy to take place. The outcomes indicate that both processes have high activation energies (25.72–28.27 kcal mol^{-1} when n = 2 and 37.25–39.68 kcal mol^{-1} when n = 3), low Gibbs energies and are moderately exothermic. As a result, these reactions might not occur under microwave irradiation. Moreover, the polarity only increases slightly from the ground to the transition state.

The question remains—why does the reaction take place? The presence of the ionic liquid may have a strong influence on the polarity of the medium and we therefore analyzed the geometric and electronic structure of bmimPF$_6$. Based on a previous report[24] we performed a conformational study of the ionic liquid. Multiple stable structures for the [C$_4$C$_1$im]Cl ion pair were obtained previously. The chloride has seven possible locations, *Front-Methyl*, *Front-Butyl*, *Butyl-side*, *Methyl-side* and *Back* on the plane of the imidazole ring and *Upper side* and *Lower side* of the imidazole ring (Fig. 4).

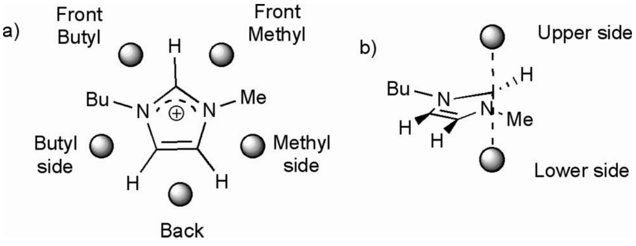


Fig. 4 Location of primary cation–anion interaction sites for [C$_4$C$_1$im]Cl: (a) Cl anion in-plane; (b) Cl anion out-of-plane.

In our case, we explored the most stable conformers of bmimPF$_6$ at the B3LYP/6-31+G* level and observed that motion of the counteranion is easy. Three stable conformers were found in which the PF$_6$ anion is close to the methyl and butyl groups. The main geometric features of these conformers are depicted in Fig. 5 and the polarity data are given in Table 7.

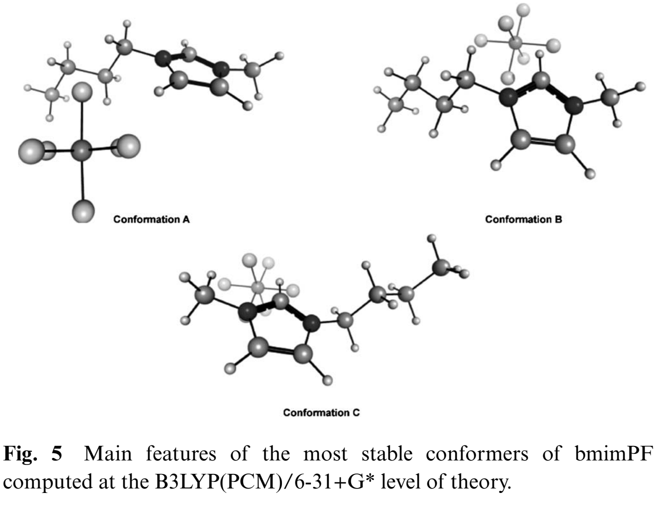


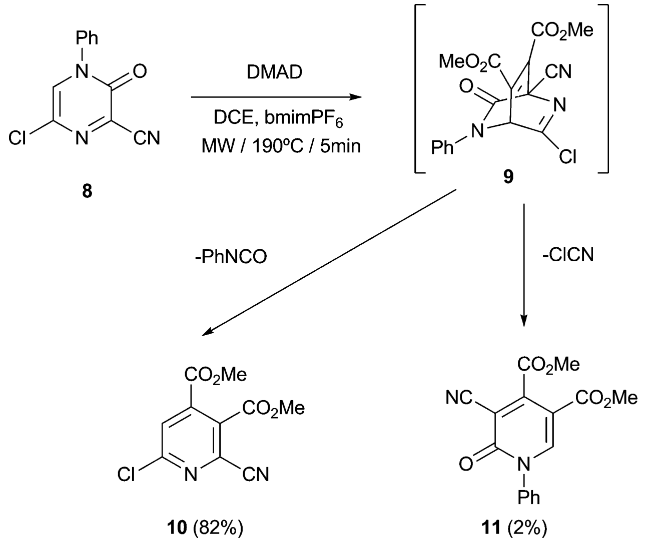
Fig. 5 Main features of the most stable conformers of bmimPF$_6$ computed at the B3LYP(PCM)/6-31+G* level of theory.

These results show that, in spite of the energetic parameters, the reaction occurs due to the polarity of the reagents and the ionic liquid, which may act as a microwave susceptor. Alkenyl-tethered 2(1*H*)-pyrazinones **6a–b** are more polar than those in our previously studied IMDA reaction (5.23 and 5.11 D, respectively) and they are special due to the high polarity of the ionic liquid (18 D), which can couple very effectively with microwaves through an ionic conduction mechanism. Therefore, small amounts of an ionic liquid can be employed as additives in order to increase the dielectric constant and therefore enhance the Diels–Alder cycloaddition reaction.

Table 7 Dipole moments (μ, D) of the most stable conformers of bmimPF$_6$ computed at B3LYP(PCM)/6-31+G*+ΔZPVE

Entry	Conformer	μ (D)
1	A	18.14
2	B	17.56
3	C	18.84

We next turned our attention to intermolecular reactions of 2(1*H*)-pyrazinones **8** with dimethyl acetylenedicarboxylate (DMAD). These Diels–Alder reactions generally led to mixtures of pyridines and pyridones through two competing spontaneous retro-Diels–Alder fragmentation pathways from the initially formed bicyclic cycloadducts (Scheme 4). Pyrazinone **8** reacts with DMAD to afford pyridine **10** and pyridone **11** in 82% and 2% isolated yield, respectively, after only 5 min of microwave irradiation. These results are consistent in terms of product yields and ratios with the data obtained under thermal conditions where DMAD was also used as the solvent under reflux conditions (140 °C, 30 min).



Scheme 4

In this reaction, microwave irradiation did not produce a great improvement in the reaction and only a small reduction in the reaction time was observed. Our theoretical results, collected in Tables 8 and 9, indicate that this cycloaddition has a very low activation energy (20.57 kcal mol^{-1}). Thus, reactions with an activation energy of around 20 kcal mol^{-1} can be carried out successfully both by microwave and by classical heating. As a consequence, an improvement should *not* be expected on using microwave irradiation.

Moreover, the energy requirement of the retro-Diels–Alder process leading to pyridine **10** is lower than that required for the

Table 8 Diels–Alder reaction of compound **8** and DMAD. Activation energy (Δ*E*a, kcal mol^{-1}), Gibbs energy (Δ*G*, kcal mol^{-1}) and enthalpy energy (Δ*H*, kcal mol^{-1}) computed at B3LYP(PCM)/6-31G*+ΔZPVE

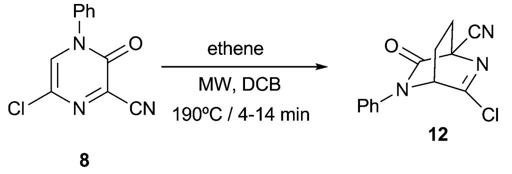
Entry	Reaction	Δ*E*a	Δ*G*	Δ*H*
1	**8** → **9**	20.57	−0.01	−23.42
2	**9** → **10**	22.09	−52.12	−30.11
3	**9** → **11**	30.70	−30.28	−10.76

Table 9 Diels–Alder reaction of compound **8** and DMAD. Volume (*a*0, Å), dipole moments (*μ*, D), average polarizability volumes (α'_{av}, Bohr^3), hardnesses (*η*, eV) of reagents, transition structures and products computed at B3LYP(PCM)/6-31G*+ΔZPVE

Entry	Stationary point	*a*0 (Å)	*μ* (D)	α'_{av} (Bohr^3)	*η* (eV)	Δ*μ* (D)
1	**8**	4.81	8.30	148.58	0.067	
2	**9**	5.08	8.90	209.10	0.077	
3	**TS9**	5.28	6.83	229.56	0.065	−1.47
4	**TS10**	5.39	6.09	230.39	0.071	−2.81
5	**TS11**	5.52	6.96	230.89	0.057	−1.94
6	**10**	5.37	6.50	197.63	0.079	
7	**11**	5.01	5.19	138.02	0.096	

Diels–Alder pathway leading to pyridone **11** (Table 8, entry 2 *vs.* 3), which justifies why pyridine **10** is obtained with a higher yield.

The third cycloaddition route involved the Diels–Alder cycloaddition reaction of pyrazinone **8** with ethene (Scheme 5), which gives the bicyclic cycloadducts **12**. Under conventional conditions, this cycloaddition reaction was carried out in an autoclave with an ethene pressure of 25 atm before the setup was heated to 110 °C for 12 h. Under microwave irradiation, the conditions were changed because the presence of the ionic liquid caused spontaneous decomposition of the reaction mixture. Therefore, a suitable solvent, 1,2-dichlorobenzene (DCB), was chosen as a microwave absorber, which allowed the cycloaddition chemistry to be carried out in the range 180–250 °C through microwave flash heating. The reaction took place in a sealed microwave vial during 40 min at 190 °C and gave 86% isolated yield of pure cycloadduct **12** (82% under conventional thermal conditions). Once again, the reaction was carried out under very harsh conditions and required 12 h to reach completion. In this case, there is a dramatic improvement under microwave irradiation.



Scheme 5

The potential surface of this reaction was explored at the B3LYP(PCM)/6-31G*+ΔZPVE level using DCB as solvent. The resulting energetic features and physical properties of the stationary points are collected in Tables 10 and 11.

Once again, the low activation energy (21.59 kcal mol^{-1}) indicates that microwave irradiation would not produce a significant improvement. However, as the reaction is endothermic (Δ*H* = 11.46 kcal mol^{-1}), microwave irradiation may have beneficial influence because the short reaction time under microwaves may avoid the reversibility of the cycloaddition.

Table 10 Diels–Alder reaction of compound **8** and ethene. Activation energy (Δ*E*a, kcal mol^{-1}), Gibbs energy (Δ*G*, kcal mol^{-1}) and enthalpy energy (Δ*H*, kcal mol^{-1}) computed at B3LYP(PCM)/6-31G*+ΔZPVE

Entry	Δ*E*a	Δ*G*	Δ*H*
1	21.59	−11.22	11.46

Table 11 Diels–Alder reaction of compound **8** and ethene. Volume (*a*0, Å), dipole moments (*μ*, Δ), average polarizability volumes (α'_{av}, Bohr^3), hardnesses (*η*, eV) of reagents, transition structures and products computed at B3LYP(PCM)/6-31G*+ΔZPVE

Entry	Stationary point	*a*0 (Å)	*μ* (D)	α'_{av} (Bohr^3)	*η* (eV)	Δ*μ* (D)
1	**8**	4.81	8.30	148.58	0.067	
2	**TS12**	5.25	8.28	169.78	0.077	−0.02
3	**12**	4.75	8.04	153.95	0.099	

The stationary points are highly polar, although there is no significant increase in the polarity along the reaction coordinate.

Conclusions

In this study we performed a complete DFT study on IMDA reactions of 2-cyano-substituted *N*-alkyl azadiene and intra- and intermolecular reactions of alkenyl-tethered 2(1*H*)-pyrazinones.

These reactions were chosen because the rapid heating produced by microwave irradiation can overcome some of the drawbacks of Diels–Alder reactions (long reaction times at high temperatures and sometimes high pressures are required). The applicability of Diels–Alder reactions is therefore limited by the reversibility of the reaction when a long reaction time is required.

Our aim was to use computational calculations as predictive tools to determine when a reaction can be improved under microwave conditions.

The results obtained show that the activation energy of the reaction and the polarity of the stationary points are good indicators of this possibility. The following conclusions can be drawn:

- The presence of any component with high polarity allows a very effective interaction with microwaves through an ionic conduction mechanism.
- Reactions with activation energies below 20 kcal mol^{-1} occur easily by conventional heating and improvements are not expected under microwaves. Microwave irradiation may have a beneficial effect if these processes are endothermic.
- Reactions with activation energies from 20 to 30 kcal mol^{-1} can be improved under microwave irradiation without the use of harsh reaction conditions (*e.g.*, high pressure, pyrolysis).
- Reactions with activation energies above 30 kcal mol^{-1} cannot be performed either under conventional heating or microwave irradiation. However, the use microwave susceptors such as ionic liquids or highly polar solvents (microwave flash heating) can improve these processes.

The main conclusions of this study are summarized in the following table.

ΔEa	ΔH	Conclusions
< 20 kcal mol^{-1}	< 0	Not improved
	> 0	Improved
20–30 kcal mol^{-1}	< 0	Improved
	> 0	Improved
30 kcal mol^{-1}		Do not occur
		Improved with susceptors

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